IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

In re Entresto (Sacubitril/Valsartan) Patent Litigation	C.A. No. 20-2930-RGA [redacted]
NOVARTIS PHARMACEUTICALS CORPORATION, Plaintiff, v. MSN PHARMACEUTICALS INC., MSN LABORATORIES PRIVATE LIMITED, MSN LIFE SCIENCES PRIVATE LIMITED, GERBERA THERAPEUTICS, INC., NANJING NORATECH PHARMACEUTICAL CO., LIMITED, Defendants.	C.A. No. 22-1395-RGA [redacted]

OPENING BRIEF IN SUPPORT OF
NOVARTIS'S MOTION FOR INJUNCTIVE RELIEF AGAINST MSN

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OF COUNSEL:

Nicholas N. Kallas
Christina Schwarz
Christopher E. Loh
Jared L. Stringham
VENABLE LLP
151 West 42nd Street
New York, New York 10036
(212) 307-5500

Daniel O'Brien (#4897)
VENABLE LLP
1201 N. Market St, Suite 1400
Wilmington, Delaware 19801
(302) 298-3535
daobrien@venable.com

Attorneys for Plaintiff Novartis Pharmaceuticals Corporation

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TABLE OF ABBREVIATIONS

'918 patent	U.S. Patent No. 11,096,918 assigned to Novartis
amorphous TVS	amorphous trisodium valsartan-sacubitril (complex)
ANDA	abbreviated new drug application
API	active pharmaceutical ingredient
cm^{-1}	Wavenumber
crystalline TVS	crystalline trisodium valsartan-sacubitril (complex)
DiMeo	Declaration of Daniel DiMeo in Support of Novartis's Motion for Injunctive Relief Against MSN
DSC	differential scanning calorimetry
Ex. __	Exhibit accompanying Novartis's Motion for Injunctive Relief against MSN
FF __	the numbered paragraph(s) of Plaintiff Novartis Pharmaceuticals Corporation's Findings of Fact for U.S. Patent No. 11,096,918 (20-md-2930, D.I. 1706)
IR	infrared spectroscopy
Jarosz	Declaration of John C. Jarosz in Support of Plaintiff's Motion for Injunctive Relief Against MSN
mg	Milligram
MSN	MSN Pharmaceuticals Inc., MSN Laboratories Private Limited, and MSN Life Sciences Private Limited
MSN Post-trial Br.	Defendants' Answering Brief Regarding Non-infringement of the '918 Patent (20-md-2930, D.I. 1757)
MSN's ANDA	MSN's ANDA No. 213748
MSN's ANDA products or MSN tablets	generic sacubitril/valsartan tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg, described in MSN's ANDA No. 213748
Novartis	Novartis Pharmaceuticals Corporation
POSA	person of ordinary skill in the art
R&D	research and development
Raman	Raman spectroscopy
ssNMR	solid state nuclear magnetic resonance
Tr.	December 9-13, 2024 trial transcripts for MDL No. 20-2930-RGA, C.A. No. 23-401-RGA, and C.A. No. 22-1395-RGA
_TX	admitted trial exhibit from the December 9-13, 2024 trial
TVS	trisodium valsartan-sacubitril (complex)
UF __	Joint Statement of Undisputed Facts Regarding the '918 Patent (20-md-2930, D.I. 1641, Exhibit 1A)
XRPD	X-ray powder diffraction

I. INTRODUCTION

Novartis moves for a preliminary injunction against MSN to prevent the at-risk launch of MSN's ANDA products, which are generic versions of Novartis's Entresto® heart failure drug products, pending this Court's trial decision and entry of final judgment for U.S. Patent No. 11,096,918 (the "'918 patent"). If the Court decides infringement in Novartis's favor, 35 U.S.C. § 271(e)(4)(A) requires an order resetting MSN's effective ANDA approval date to November 9, 2026, the day after the '918 patent expires. *See* 20-md-2930, D.I. 1878. Such a reset order before July 15, 2025 would prevent MSN's at-risk launch. Because, as explained herein, Novartis proved at trial by a preponderance of evidence that MSN infringes the '918 patent, an at-risk launch by MSN will deprive Novartis of its statutory reset order, thereby causing immediate and irreparable harm to Novartis by the loss of that Congressionally mandated relief as well as due to the likely irrecoverable loss of Entresto®'s formulary position, irreversible price erosion, and harm to Novartis's reputation and goodwill.

If the Court does not intend to issue a decision and enter final judgment before July 15, 2025, Novartis requests that this Court temporarily enjoin MSN from commercial marketing and sale of its ANDA products until final judgment is entered to prevent irreparable harm to Novartis. Novartis also moves for a temporary restraining order against MSN if a decision on Novartis's preliminary injunction motion is not issued by July 15, 2025. Last, if the Court denies this preliminary-injunction request or issues a final judgment against Novartis on the merits, Novartis requests an injunction pending appeal under Fed. R. Civ. P. 62(d) based on the factors addressed herein—or at least a 72-hour temporary injunction to seek relief from the Federal Circuit.

II. BACKGROUND

Novartis in October 2022 sued MSN under 35 U.S.C. § 271(e)(2) for infringement of the

'918 patent, which claims an amorphous trisodium valsartan-sacubitril complex ("amorphous TVS"), because MSN seeks to commercially market and sell its ANDA products before the '918 patent's November 8, 2026 expiration date. Even though the '918 patent is not Orange Book-listed, a generic drugmaker can still infringe a non-Orange Book-listed patent under § 271(e)(2) by filing an ANDA. *See, e.g.*, *Glaxo Grp. Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1344 (Fed. Cir. 2004); *Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1123-24 (Fed. Cir. 2018); *Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 642 F. Supp. 2d 329, 363 n. 49 (D. Del. 2009). Because MSN infringes under § 271(e)(2), 35 U.S.C. § 271(e)(4)(A) requires entry of an order resetting the effective approval date of MSN's ANDA until after the '918 patent expires, and the Court should also provide temporary injunctive relief pursuant to 35 U.S.C. § 271(e)(4)(B) until MSN's effective approval date is reset to after November 8, 2026.

The December 9-13, 2024 trial[1] was limited to infringement as MSN did not challenge validity. Tr. 1035:17-23. Post-trial briefing was completed on February 7, 2025.

On April 1, 2025, this Court entered final judgment that a different patent—U.S. Patent No. 8,101,659—was infringed and not invalid, reset MSN's ANDA approval date to no earlier than July 16, 2025, and enjoined MSN from commercial marketing and sale until FDA resets MSN's ANDA approval. 20-md-2930, D.I. 1824. MSN thus cannot launch before July 16, 2025 because its ANDA has been reset to tentative approval. But because MSN has repeatedly indicated it will launch "at the earliest available date" (*see, e.g.*, Appeal No. 25-1722, D.I. 16-1 (MSN May 9, 2025 Brief) at 9), Novartis believes that MSN will launch any time on or after July 16 that it has FDA approval and is not enjoined, thereby necessitating this injunction motion.

[1] Defendants Nanjing Noratech Pharmaceutical Co., Ltd. and Gerbera Therapeutics, Inc. (collectively, "Noratech") also participated in the December 9-13, 2024 trial.

III. ARGUMENT

35 U.S.C. § 283 gives district courts authority to "grant injunctions in accordance with the principles of equity." "A decision to grant or deny a preliminary injunction is within the sound discretion of the district court, based upon its assessment of four factors: (1) the likelihood of the patentee's success on the merits; (2) irreparable harm if the injunction is not granted; (3) the balance of hardships between the parties; and (4) the public interest." *Tinnus Enters., LLC v. Telebrands Corp.*, 846 F.3d 1190, 1202 (Fed. Cir. 2017). The same factors "also apply to temporary restraining orders" and Rule 62(d) motions. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, No. 09-MD-2118, 2011 WL 1980610, at *1 (D. Del. May 20, 2011); *Standard Havens Prods. v. Gencor Indus.*, 897 F.2d 511, 512-13 (Fed. Cir. 1990). The likely success and irreparable harm factors are "the most critical" factors to evaluate (*Nken v. Holder*, 556 U.S. 418, 434 (2009)); however, all four factors favor a preliminary injunction here.

This Court's August 2024 denial of Novartis's prior preliminary injunction motion on the pretrial factual record, and the Federal Circuit's affirmance thereof, do not preclude relief here because this Court subsequently held a complete merits trial, and this motion is based on that factual evidence. *Cf. Univ. of Tex. v. Camenisch*, 451 U.S. 390, 395 (1981) (preliminary injunction fact findings, based on "procedures that are less formal and evidence that is less complete than in a trial on the merits," "are not binding"). The Federal Circuit also subsequently enjoined MSN's launch based on other Novartis rights, thus recognizing the irreparable harm from a premature launch. Appeal No. 23-2218, D.I. 127.

A. Novartis Is Likely to Succeed on the Merits

To establish a likelihood of success on the merits, a patentee "must show that it will likely prove infringement, and that it will likely withstand challenges, if any, to the validity of the patent."

Tinnus, 846 F.3d at 1202 (quoting *Titan Tire Corp. v. Case New Holland, Inc*., 566 F.3d 1372, 1376 (Fed. Cir. 2009)). Furthermore, Novartis need only show infringement by a preponderance of the evidence. *Purdue Pharma*, 642 F. Supp. 2d at 362 (citing *Catalina Lighting, Inc. v. Lamps Plus, Inc.,* 295 F.3d 1277, 1285 (Fed. Cir. 2002)). As explained below, Novartis proved at trial that MSN infringes the '918 patent claim 1, and MSN did not challenge validity.

1. MSN Infringes the '918 Patent

The Court's claim construction requires that amorphous TVS "predominate" over the crystalline form of TVS in MSN's tablets. FF[2] 5; UF 21; Tr. 478:5-22 (Matzger). A POSA would understand that the construction distinguishes the claimed amorphous TVS "compound" from the unclaimed crystalline TVS. But amorphous TVS need not "predominate" over any physical mixture of valsartan disodium and sacubitril sodium, or excipients of a tablet, which are not the TVS "compound" recited in claim 1. UF 23-24; Tr. 478:15-479:25, 569:11-19 (Matzger). Thus, for MSN to infringe claim 1 under this Court's construction, Novartis must prove (as it did at trial) that (1) MSN's tablets contain amorphous TVS, and (2) the amorphous TVS in MSN's tablets "predominates" over the crystalline form of TVS. Because MSN continues to maintain (incorrectly) that its API is a crystalline TVS complex, Novartis first addresses the nature of MSN's crystalline API and then addresses the presence of amorphous TVS in MSN's tablets.

a) Because MSN's Tablets Do Not Contain Crystalline TVS, Amorphous TVS Necessarily "[P]redominates"

MSN's API manufacturing process cannot produce crystalline TVS. And Novartis's expert Dr. Matzger proved by multiple tests that MSN's crystalline API both before and after it is incorporated into MSN's tablets is not crystalline TVS. Therefore, because crystalline TVS is non-

[2] Novartis references its post-trial Findings of Fact ("FF") for the Court's convenience, however, Novartis also references the trial evidence to avoid any improper incorporation by reference.

existent in MSN's tablets, amorphous TVS "predominates" over that non-existent crystalline TVS.

MSN makes its crystalline API by mixing physically separate valsartan disodium and sacubitril sodium in a liquid, n-heptane. FF 222; Tr. 516:3-517:4 (Matzger); Ex. 107 (PTX 1523) at MSNSV_023281-282. Because valsartan disodium and sacubitril sodium cannot dissolve in n-heptane, the physically separate valsartan and sacubitril cannot interact to form a crystalline TVS complex. Tr. 516:3-517:4 (Matzger); Ex. 105 (PTX 1521) at MSNSV_023049; Ex. 106 (PTX 1522) at MSNSV_023200, 206. Thus, MSN's manufacturing process demonstrates that MSN's crystalline API is a physical mixture, not a crystalline TVS complex. *Id.* Neither MSN nor its expert Dr. Steed disputed, let alone rebutted, this evidence. That alone should end this inquiry.

Three sets of testing by Dr. Matzger and one by MSN's own third-party laboratory EAG further prove that MSN's crystalline API before and after incorporation into MSN's tablets is a crystalline physical mixture, not a crystalline TVS complex.

If MSN's crystalline API was a crystalline TVS complex, as MSN and Dr. Steed alleged, test data for all of MSN's crystalline API samples would be the same regardless of the sample used. This is because a TVS complex contains a fixed 1:1 ratio of valsartan to sacubitril at every location within a sample, whereas the valsartan-to-sacubitril ratio at different locations in a physical mixture will vary. FF 103, 213, 219; Tr. 476:24-477:21, 510:12-17; 584:17-585:22 (Matzger); Ex. 111 (PTX 1719) at 1-3. As summarized below, multiple tests show that MSN's crystalline API differs in the ratio of valsartan to sacubitril from one location to another or from one particle (*i.e.*, a single grain containing numerous molecules) to another, proving that MSN's crystalline API is not a crystalline TVS complex but instead is a heterogenous physical mixture.[3]

[3] (1) FF 189, 209-216; Tr. 511:8-19 (Matzger); Ex. 112 (PTX 1720); Ex. 113 (PTX 1721); (2) FF 173, 176, 221; Tr. 487:7-21, 493:13-497:20; 508:8-12, 515:3-516:2 (Matzger); (3) FF 217-220;

(1) Raman mapping on MSN's crystalline API outside of tablet	Raman maps show separate green and red areas corresponding to physically separate crystalline valsartan disodium and crystalline sacubitril sodium.
(2) Raman mapping on MSN's tablets	Raman maps show separate green and red areas corresponding to physically separate crystalline valsartan disodium and crystalline sacubitril sodium.
(3) X-ray microdiffraction on MSN's crystalline API outside of tablet	X-ray patterns on different particles of MSN's API show significantly different peak intensities or heights compared to each other and a bulk sample of MSN's crystalline API.
(4) EAG's Raman testing on MSN's crystalline API outside of tablet	Spectra on two different MSN API samples show different peaks and peak intensities corresponding to physically separate crystalline valsartan disodium and crystalline sacubitril sodium.

As explained in Section III(A)(1.a.i.a) below, MSN's counter arguments do not rebut the preponderance of evidence demonstrating that MSN's crystalline API is a physical mixture.

b) MSN's Tablets Contain Amorphous TVS

i) Dr. Park's Amorphous TVS Standard Is Appropriate

As explained below, to prove that MSN's tablets contain amorphous TVS, Novartis's expert Dr. Park first prepared the "glassy solid" (*i.e.*, amorphous TVS) according to Example 1 of the '918 patent and then generated a reference, *i.e.*, "fingerprint," spectrum for that amorphous TVS. Dr. Matzger then used a well-known analytical technique called Raman mapping to collect data from MSN's tablets and compared that Raman map data to Dr. Park's amorphous TVS fingerprint spectrum to identify the presence of amorphous TVS in MSN's tablets.

A complex differs from a physical mixture due to weak non-covalent bonds holding the valsartan and sacubitril together in the complex, which bonds do not exist in a physical mixture. Tr. 376:5-16, 435:12-436:12 (Park); Tr. 476:16-477:21 (Matzger). The '918 patent specification teaches that the amorphous TVS complex can be distinguished from a physical mixture of amorphous valsartan disodium and amorphous sacubitril sodium ("amorphous physical mixture")

Tr. 513:9-514:14 (Matzger); Ex. 114 (PTX 1723); (4) FF 227; Tr. 537:9-538:6 (Matzger); Ex. 117 (PTX 1728) at 1-3; Ex. 118 (DTX 792-S).

by "very distinct spectral peaks and shifts that are not observed in the physical mixture." Tr. 376:19-377:14 (Park); Ex. 1 (JTX 3) at 16:40-55, 17:41-58. Those distinct spectral peaks and shifts are caused by the non-covalent bonds between valsartan and sacubitril in a complex and can be detected using spectroscopic techniques such as ssNMR, IR, and Raman disclosed in the '918 patent. Tr. 377:15-24, 381:25-382:20 (Park); Ex. 1 (JTX 3) at 20:43-21:3, 30:23-31:25.

Neither MSN nor its experts disputed Dr. Park's ssNMR and IR spectra for the glassy solid, showing at least three distinct peaks and shifts compared to the respective spectra for amorphous valsartan disodium and amorphous sacubitril sodium (ssNMR), and the amorphous physical mixture (IR). FF 9, 34-35, 41; Tr. 373:4-11 (Park). It is also undisputed that Dr. Park's XRPD spectrum proved that the glassy solid is amorphous. Tr. 373:4-8, 384:6-12 (Park); Ex. 6 (PTX 1268). Thus, the undisputed evidence confirms that the glassy solid that Dr. Park prepared according to Example 1 is amorphous TVS.

Dr. Park's Raman spectrum for the glassy solid (*i.e.*, amorphous TVS) also showed at least three distinct peaks and shifts compared to the Raman spectrum for the amorphous physical mixture, which indicates the presence of non-covalent hydrogen bonds between valsartan and sacubitril in the glassy solid that are not present in the amorphous physical mixture:

Amorphous Physical Mixture	**Glassy Solid**	**Shift**
1283.4 cm^{-1}	1287.2 cm^{-1}	3.8 cm^{-1}
1600.6 cm^{-1}	1603.4 cm^{-1}	2.8 cm^{-1}
1611.2 cm^{-1}	1614.0 cm^{-1}	2.8 cm^{-1}

FF 9, 36; Tr. 394:15-395:17 (Park); Ex. 7 (PTX 1277). These shifts are real differences because they exceed the ±1 cm^{-1} error for Dr. Park's Raman instrument. FF 59; Tr. 415:20-25 (Park).

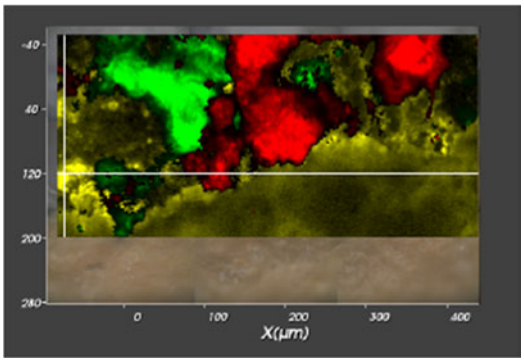
In sum, Dr. Park's testing proves the glassy solid of Example 1 is amorphous TVS and her fingerprint Raman spectrum for amorphous TVS is a reliable reference to identify amorphous TVS in MSN's tablets. As explained in Section III(A)(2b) below, MSN's counter arguments do not

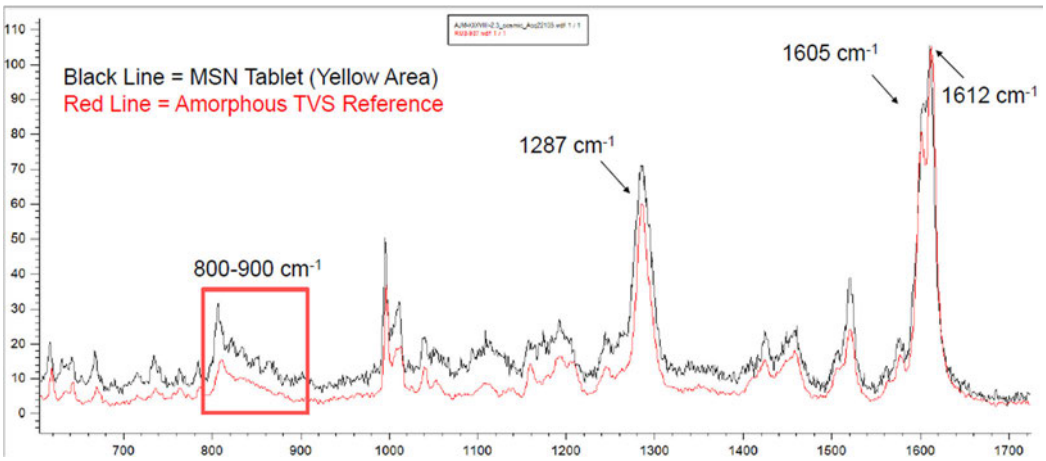
rebut the preponderance of evidence demonstrating the reliability of Dr. Park's Raman spectrum.

ii) Dr. Matzger's Testing Proves that MSN's Tablets Contain Amorphous TVS

Dr. Matzger tested representative samples of all three dosage strengths of MSN's tablets using Raman mapping, whereby he collected tens of thousands of experimental Raman spectra from those samples. FF 92-93, 169; Tr. 489:20-490:20, 493:13-494:17, 519:22-520:5 (Matzger); Ex. 115 (PTX 1726) at 1. Dr. Matzger compared the Raman mapping spectra from MSN's tablets to Dr. Park's fingerprint spectrum of amorphous TVS and proved that amorphous TVS is present in MSN's tablets. FF 33-41, 170; Tr. 378:4-379:25 (Park); 487:7-21, 492:7-10, 503:17-22 (Matzger). Because MSN's three dosage strengths contain the same ingredients in similar ratios and are manufactured in similar ways, if amorphous TVS is present in one dosage strength of MSN's tablets, then amorphous TVS is present in all three dosage strengths of MSN's tablets. FF 164; Tr. 485:24-486:10 (Matzger); Ex. 102 (JTX 200) at MSNSV_000234-35.

Dr. Matzger demonstrated that amorphous TVS is present in MSN's 49/51 mg tablets by comparing a Raman map spectrum from the yellow areas (shown below) in his Raman map (corresponding to areas of the tablet with substantial contributions from the amorphous TVS reference Raman spectrum) to Dr. Park's fingerprint Raman spectrum for amorphous TVS, and determining that they are a good match because every peak in that fingerprint Raman spectrum is present in Dr. Matzger's Raman map spectrum (including features characteristic of amorphous TVS: peaks at about 1287, 1605, and 1612 cm^{-1}, as well as a lack of well-defined peaks between 800 to 900 cm^{-1}). Tr. 497:21-499:5 (Matzger); Ex. 108 (PTX 1709) at 3.





Dr. Matzger similarly identified yellow areas in his Raman maps for MSN's 97/103 mg and 24/26 mg tablets that can only be explained by the presence of amorphous TVS. FF 182-185; Tr. 503:23-505:20, 506:5-507:6 (Matzger); Ex. 109 (PTX 1710) at 3; Ex. 110 (PTX 1711) at 3.

As explained in Section III(A)(2b) below, MSN's counter arguments do not rebut the preponderance of evidence demonstrating that MSN's tablets contain amorphous TVS.

2. <u>MSN Did Not Rebut the Preponderance of Infringement Evidence</u>

a) Dr. Steed's Testimony that MSN's Crystalline "Form-S" API Is a Crystalline TVS Complex Is Without Merit

Dr. Steed testified at trial that MSN's crystalline "Form-S" API is a crystalline TVS complex. Tr. 986:18-24 (Steed). But neither MSN nor Dr. Steed disputed that MSN's API n-heptane manufacturing process is incapable of forming a crystalline complex. *Supra* Section III(A)(1a). Instead, Dr. Steed argued that "Form-S" is a crystalline TVS complex because: (i) crystalline valsartan disodium and crystalline sacubitril sodium overlap in certain areas in Dr. Matzger's Raman maps ("Raman map overlaps") (Tr. 934:9-935:11 (Steed)); (ii) differences in Dr. Matzger's X-ray patterns could be due to preferred orientation or to differences in the texture, stress, or crystallinity between the two particles ("X-ray differences") (Tr. 995:11-22 (Steed)); (iii) EAG's Raman spectra for MSN's crystalline API have a peak at 1281 cm^{-1}, allegedly different from a physical mixture ("EAG's Raman spectra") (Tr. 991:8-992:17 (Steed)); and (iv) an alleged

single melting point in MSN's DSC data for its crystalline API ("MSN's DSC data") shows that it is a complex (Tr. 987:21-990:2 (Steed)). None of Dr. Steed's arguments, addressed below, rebuts the preponderance of evidence demonstrating that MSN's crystalline API is a physical mixture.

(i) Raman map overlaps: The overlapping presence of both crystalline valsartan disodium and crystalline sacubitril sodium in certain areas of Dr. Matzger's Raman maps for MSN's crystalline API and tablets just proves that those two components are present in those areas of Dr. Matzger's Raman maps, not that they are complexed. FF 103, 216; Tr. 476:24-477:21, 508:25-509:6, 509:17-510:22, 510:18-22, 681:20-682:18 (Matzger). Dr. Matzger demonstrated that a crystalline physical mixture can have areas where crystalline valsartan disodium and crystalline sacubitril sodium overlap; however, there are also significant areas where there is no overlap, which can only be explained by a physical mixture. FF 213, 216; Tr. 509:17-510:22 (Matzger). As explained in Section III(A)(1)(a) above, a TVS complex will always have a fixed 1:1 ratio of valsartan to sacubitril, unlike MSN's crystalline physical mixture containing varying valsartan-to-sacubitril ratios as Dr. Matzger's testing demonstrated.

(ii) X-ray differences: Dr. Steed did not dispute that there are clear differences between Dr. Matzger's X-ray patterns for two different particles of MSN's crystalline API. Tr. 994:16-995:10 (Steed). Those differences can only be caused by varying ratios of valsartan and sacubitril demonstrating that MSN's crystalline API is a physical mixture. FF 220; Tr. 513:9-514:14 (Matzger). Dr. Steed is wrong that those differences could be due to preferred orientation or to differences in the texture, stress, or crystallinity between the two particles because Dr. Matzger used a "Gandolfi" apparatus to eliminate preferred orientation effects, and he did not change the texture, stress, or crystallinity of the tested particles in any manner. FF 224; Tr. 534:6-536:6 (Matzger). Dr. Steed did not rebut Dr. Matzger's testimony on those points.

(iii) EAG's Raman spectra: As discussed in Section III(A)(a) above, EAG's Raman spectra of two samples of MSN's crystalline API prove that they are physical mixtures because the peaks and peak intensities of the two spectra differ. Those differences will not arise in a complex; they arise only in a physical mixture. FF 227, 228; Tr. 537:9-538:3 (Matzger); Ex. 117 (PTX 1728). Moreover, that Dr. Steed observed a common peak at 1281 cm^{-1} in both of EAG's spectra for MSN's crystalline API does not prove that MSN's crystalline API is a crystalline TVS complex. MSN itself admits that a single peak is insufficient to identify a substance by Raman. *See* 20-md-2930, D.I. 1757 (MSN Post-trial Br.) at 38, *citing Merck Sharp & Dohme Corp. v. Amneal Pharms. LLC*, 235 F. Supp. 3d 625, 635 (D. Del. 2017). As Dr. Matzger explained, the 1281 cm^{-1} peak is due to the presence of separate crystalline sacubitril sodium, which generates a peak at about 1278 cm^{-1} in Dr. Matzger's Raman spectrum; the difference between the 1278 and 1281 cm^{-1} peak positions is due to EAG applying baseline correction to its Raman spectra and collecting its Raman spectra in extended scan mode, causing shifting of peak positions, versus Dr. Matzger collecting his Raman spectrum for crystalline sacubitril sodium in static scan mode. FF 229; Tr. 539:17-541:5 (Matzger). Dr. Steed did not rebut Dr. Matzger's testimony on those points.

(iv) MSN's DSC data: The alleged 131°C melting point on which Dr. Steed relied does not demonstrate that MSN's crystalline API is a TVS complex because Dr. Steed failed to consider, let alone rebut, the following alternative explanations for the melting point of MSN's crystalline API: (i) multiple polymorphs of individual crystalline sacubitril sodium and individual crystalline valsartan disodium have melting points at about 131°C—thus, a physical mixture can have a 131°C melting point (Ex. 116 (PTX 1727) at 1; Ex. 8 (PTX 1664) at 6:11-7:41; Ex. 9 (PTX 1665) at 2:4-3:61); (ii) the melting point of a physical mixture can be reduced by the presence of water in the sample and/or a phenomenon called melting point depression (Ex. 10 (PTX 1666; Ex. 11 (PTX

1667) at 3968; Ex. 103 (JTX 206) at MSNSV_37399); and (iii) the large difference between the energy required to allegedly melt MSN's crystalline API in comparison to the much greater amount of energy required to melt a crystalline TVS complex indicates that MSN's API is not a crystalline TVS complex (Ex. 104 (JTX 209) at MSNSV3_000539; Ex. 101 (JTX 140) at NPC-VS-016626495). FF 234; Tr. 546:14-551:4 (Matzger).

Thus, a preponderance of evidence proves MSN's crystalline API is a physical mixture.

b) MSN Fails to Undermine Novartis's Showing that MSN's Tablets Contain Amorphous TVS

i) Dr. McCreery's Testimony Criticizing Dr. Park's Fingerprint Raman Spectrum Is Without Merit

MSN's expert Dr. McCreery testified that Dr. Park's fingerprint Raman spectrum for amorphous TVS—on which Dr. Matzger relied to identify amorphous TVS in MSN's ANDA products—is unreliable because: (i) it is "impossible" for a Raman spectrum of amorphous TVS to look like Dr. Park's amorphous TVS spectrum (Tr. 757:1-9 (McCreery)); (ii) Dr. Park's amorphous TVS spectrum looks no different than her spectrum for the amorphous physical mixture (Tr. 727:17-730:2 (McCreery)); and (iii) any differences between those two spectra are the result of an alleged calibration error with Dr. Park's Raman instrument (Tr. 727:12-16, 752:20-24 (McCreery)). Leaving aside Dr. Park's Raman data, neither Dr. McCreery nor any other expert disputed that Dr. Park's ssNMR and IR data prove that her amorphous TVS sample is a complex and not a physical mixture. FF 41; Tr. 373:4-11 (Park).

Dr. McCreery's testimony concerning Dr. Park's Raman spectrum for amorphous TVS lacks substantial merit because (i) Dr. McCreery has never studied amorphous complexes and thus has no basis to opine on what an amorphous TVS Raman spectrum should look like, let alone that Dr. Park's amorphous TVS Raman spectrum is "impossible" (FF 17; Tr. 744:21-23 (McCreery)); (ii) Dr. Park's Raman spectrum for amorphous TVS only looks similar to the Raman spectrum for

the amorphous physical mixture because, as Dr. McCreery admitted on cross-examination, he deliberately manipulated Dr. Park's Raman spectra to eliminate visible differences between them (Tr. 749:21-750:14 (McCreery)); and (iii) both the calibration data for Dr. Park's Raman instrument and the internal helium-neon-laser calibration mechanism built into her instrument, which ensures that it is properly calibrated every time it is run—and which mechanism Dr. McCreery admitted was present in her instrument, Tr. 755:23-756:8 (McCreery)—prove that Dr. Park's Raman instrument did ***not*** experience any calibration error when she was testing amorphous TVS and other samples for purposes of this litigation (FF 55-62; Tr. 414:23-415:19 (Park)).

Regardless, any alleged similarity between the Raman spectra for amorphous TVS and an amorphous physical mixture is irrelevant to MSN's tablets, because Novartis and MSN agree that MSN's tablets do not contain an amorphous physical mixture. *See* Section III(A)(2)(b)(ii) belowii).

ii) Dr. Steed's Testimony Questioning the Presence of Amorphous TVS In MSN's Tablets Is Without Merit

MSN's experts Drs. Steed and McCreery at trial raised several scattershot arguments in an attempt to rebut the presence of amorphous TVS in MSN's tablets: (i) the presence of amorphous TVS in MSN's tablets is impossible based on an alleged "thermodynamically" and "kinetically" favored formation of crystalline substances over the formation of amorphous substances ("thermodynamics/kinetics") (Tr. 907:10-909:12 (Steed)); (ii) the peak positions and peak shapes in Dr. Matzger's Raman map spectra for MSN's tablets slightly differed from the four characteristic features of amorphous TVS in Dr. Park's amorphous TVS fingerprint spectrum ("peak positions/shapes") (Tr. 939:1-961:21 (Steed)); (iii); the Raman spectrum for amorphous TVS spectrum is not distinct from an amorphous physical mixture ("amorphous physical mixture") (Tr. 727:17-730:2 (McCreery)); (iv) Dr. Matzger did not provide certain statistics (a "correlation coefficient" or "goodness-of-fit"), allegedly did not provide numeric peak positions to match Dr.

Park's peak positions in her amorphous TVS fingerprint spectrum, and did not identify amorphous TVS by empty modeling ("statistics") (Tr. 922:6-926.6, 935:16-21, 941:20-24 (Steed)); and (v) Dr. Matzger allegedly did not apply the fingerprint Raman spectra for MSN's excipients or for MSN's bulk "Form-S" API to his Raman maps ("excipient and Form-S references") (Tr. 925:16-18, 929:11-15, 930:7-12 (Steed)). These arguments do not withstand the trial evidence.

(i) Thermodynamics/kinetics: Dr. Steed admitted that he performed no testing and cited no literature to support his speculation that amorphous TVS cannot form and/or will crystallize. Tr. 1020:4-19 (Steed). Contrary to Dr. Steed's speculation, Dr. Park's testing of amorphous TVS proves that it exists and Dr. Matzger's testing of MSN's tablets proves that it exists in MSN's tablets. FF 33, 170; Tr. 396:1-18, 437:7-18 (Park); Tr. 487:7-21, 489:1-9, 503:17-22 (Matzger).

(ii) Peak positions/shapes: The slight differences in peak positions or peak shapes in Dr. Matzger's Raman map spectra for MSN's tablets from Dr. Park's amorphous TVS fingerprint spectrum are irrelevant because (i) Dr. Steed has never conducted Raman mapping testing and is not qualified to testify about it (FF 186; Tr. 1004:1-18 (Steed)); (ii) as MSN's Raman mapping witness testified, the lack of a perfect match between a Raman map spectrum and a reference compound spectrum does not mean that the reference compound is absent from the Raman map (FF 101; Tr. 885:9-16, 890:14-18 (Otten)); (iii) Dr. Steed identified no material in MSN's tablets besides amorphous TVS that displays all four characteristic features of amorphous TVS (FF 197-198; Tr. 964:25-965:4 (Steed)); (iv) Dr. Steed admitted that increased noise inherent to Raman map spectra may contribute to the lack of an exact match between Dr. Matzger's amorphous TVS Raman map spectra and Dr. Park's amorphous TVS fingerprint spectrum (FF 94, 102; Tr. 941:7-8, 943:17-944:15, 948:3-25 (Steed)); and (v) Dr. Matzger explained that the additional peaks in the amorphous TVS Raman spectra taken from his MSN tablet Raman maps are due to the presence

of crystalline valsartan disodium and/or crystalline sacubitril sodium in the same pixel of the Raman map that contains amorphous TVS (FF 178, 183, 185, 202; Tr. 497:21-498:11, 503:23-505:20, 506:5-507:6 (Matzger)).

(iii) Amorphous physical mixture: The amorphous TVS Raman spectra Dr. Matzger identified in his Raman maps of MSN's tablets cannot be attributed to a physical mixture of amorphous valsartan disodium and amorphous sacubitril sodium. Dr. Steed and Dr. Matzger agree that one component of that amorphous physical mixture—amorphous sacubitril sodium—cannot persist and instead will quickly crystallize. Tr. 574:7-12; 575:20-577:17 (Matzger); Tr. 907:10-909:12, 912:3-24, 919:21-920:10 (Steed); Ex. 12 (PTX 2167); Ex. 13 (PTX 2169). Thus, any alleged similarity between the Raman spectra of the amorphous physical mixture and amorphous TVS (as alleged by Dr. McCreery) is irrelevant to Dr. Matzger's analysis of MSN's tablets. Put simply, no substance in MSN's tablets other than amorphous TVS is capable of generating the features that Dr. Matzger observed in his Raman map spectra for MSN's tablets.

(iv) Statistics: None of Dr. Steed's statistics arguments has merit: (i) Dr. Park demonstrated with literature examples that statistical analyses are not necessary to identify pharmaceutical compounds by Raman (FF 64; Tr. 422:13-423:23 (Park); Ex. 4 (PTX 1225); Ex. 5 (PTX 1228); Ex. 3 (PTX 1223); Ex. 2 (JTX 121)), and Dr. Steed cited no literature to the contrary; (ii) Dr. Matzger did consider the numeric peak positions and provided those positions in his underlying Raman data (FF 200; Tr. 498:12-499:5, 666:21-667:5 (Matzger)); and (iii) Dr. Matzger explained that empty modeling is simply a first step in the analysis and does not replace using real fingerprint spectra to identify the components in the Raman map (Tr. 643:3-8, 648:2-4 (Matzger)).

(v) Excipient and Form-S references: That Dr. Matzger allegedly did not apply fingerprint Raman spectra for MSN's excipients or MSN's bulk "Form-S" is irrelevant. None of the Raman

spectra for MSN's excipients has the four characteristic features of amorphous TVS appearing in Dr. Matzger's Raman map spectra for MSN's tablets, and do not interfere with detecting amorphous TVS. FF 174, 192; Tr. 493:13-495:22; 521:2-22 (Matzger). Because "Form-S" is a physical mixture of crystalline valsartan disodium and crystalline sacubitril sodium, the Raman spectra for different samples of "Form-S" will vary depending on the differing amounts of crystalline valsartan disodium and crystalline sacubitril sodium present in one location within the sample, and therefore there is no reliable fingerprint Raman spectrum reference for bulk "Form-S." FF 223, 227; Tr. 533:17-534:5 (Matzger). Regardless, as summarized below, Dr. Steed admitted the bulk "Form-S" Raman spectrum lacks three of the four characteristic features of amorphous TVS appearing in Dr. Matzger's Raman map spectra for MSN's tablets. FF 180, 193; Tr. 1012:8-14 (Steed); Tr. 500:8-502:20, 528:4-529:15 (Matzger); Ex. 108 (PTX 1709) at 11.

Amorphous TVS spectrum	1287 cm^{-1} peak	1605 cm^{-1} peak	800 to 900 cm^{-1}: ***no*** well-defined peaks
Bulk "Form-S" spectrum	Trough in place of 1287 cm^{-1} peak	Peak at 1598 cm^{-1}, not 1605 cm^{-1}	800 to 900 cm^{-1}: well-defined peaks

Likewise, Dr. Steed's reliance on EAG's application of EAG's Raman spectra of "Form-S" to Dr. Matzger's Raman maps for MSN's tablets to conclude that "Form-S" is present in MSN's tablets is inapposite. Tr. 976:24-980:21 (Steed). EAG did not include an amorphous TVS reference Raman spectrum and thus did not even try to search for amorphous TVS in MSN's tablets. FF 98, 204; Tr. 526:20-24, 554:16-18 (Matzger); Tr. 1023:19-1024:6 (Steed). Dr. Matzger considered EAG's "Form-S" spectrum to prove that the "Form-S" spectrum does not match the amorphous TVS Raman map spectra from MSN's tablets. FF 193; Tr. 521:25-522:7, 528:4-10 (Matzger).

Last, Dr. Matzger did not need to quantify the amount of amorphous TVS in MSN's tablets because amorphous TVS is the only form of TVS in MSN's tablets. Moreover, the presence of a small or trace amount of the claimed compound in an accused product is sufficient to find

infringement. *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1341 (Fed. Cir. 2005).

Thus, a preponderance of evidence proves that MSN's tablets contain amorphous TVS. Under Novartis's requested claim construction, which it continues to maintain should apply, that alone shows infringement. 20-md-2930, D.I.1374 at 5. Regardless, because there is no crystalline TVS in MSN's tablets, amorphous TVS necessarily "predominates" in MSN's tablets and infringes claim 1 under the Court's construction.

B. Novartis Will Suffer Irreparable Harm from an At-Risk Launch

As an initial matter, if the Court finds that MSN infringes claim 1 based on the complete trial record and enters final judgment in Novartis's favor, the Court need not address irreparable harm because 35 U.S.C. § 271(e)(4)(A) grants an order resetting the effective approval date of MSN's ANDA to a date not earlier than the expiration date of the '918 patent without any showing of irreparable harm. *Vanda*, 887 F.3d at 1138 ("[U]pon a finding of patent infringement under § 271(e)(2), the district court ***must order remedies in accordance with § 271(e)(4)***.") (emphasis added); *Janssen Prods., L.P. v. Lupin Ltd.*, No. 10-5954-WHW, 2014 U.S. Dist. LEXIS 155248 (D.N.J. Mar. 12, 2014), at *87, *93-94 (crediting patentee's argument that it would be entitled to a "mandatory order" under § 271(e)(4)(A) upon an infringement finding, notwithstanding disputes over whether patentee had shown irreparable harm). Furthermore, if MSN launches before such an order is entered, Novartis will be deprived of its statutory grant of exclusivity, which is itself irreparable harm. *Cf. Apotex Inc. v. FDA*, 508 F. Supp. 2d 78, 88 (D.D.C. 2007) ("To deny Astra [its pediatric] exclusivity period would be to deprive it of the statutorily-awarded benefit of its financial investment. . . . The erosion of Astra's statutory right is a significant harm."); *Endo Par Innovation Co., LLC v. Becerra*, No. 24-999-TJK, 2024 WL 2988904, at *6-8 (D.D.C. June 10, 2024) (finding loss of "statutory right to the 30-month stay" was irreparable because "once the

statutory entitlement has been lost, it cannot be recaptured"); *Apotex, Inc. v. FDA*, No. 06-0627-JDB, 2006 WL 1030151, at *17 (D.D.C. April 19, 2006) ("los[ing] a statutory entitlement" to 180-day exclusivity is irreparable harm; "[o]nce . . . lost, it cannot be recaptured.").

A nexus exists between the '918 patent and Novartis's irreparable harm from generic entry because MSN cannot make its products without infringing the '918 patent. *Janssen*, 109 F. Supp. 3d at 699 (finding an irreparable harm nexus for a process patent because "[w]ithout infringing the '015 Patent, Lupin would not be able to make the products proposed in its ANDA"); *Natera, Inc. v. NeoGenomics Labs., Inc.*, 106 F.4th 1369, 1380 (Fed. Cir. 2024) (patentee demonstrated nexus where infringement was a prerequisite to offering the feature that drives consumer demand). As Dr. Matzger found amorphous TVS in every sample of every dosage strength of MSN's tablets that he tested (Tr. 489:1-9, 487:7-21, 503:17-22 (Matzger); Ex. 115 (PTX 1726) at 1), the manufacturing process for MSN's tablets—specifically the coating process, which introduces water in which the active ingredients can dissolve and form an amorphous TVS complex (Tr. 491:13-492:6, 532:4-19 (Matzger))—invariably leads to the presence of amorphous TVS, the infringing compound in MSN's tablets, establishing a nexus to the '918 patent.

Entresto® is the highest earning product at Novartis, with U.S. net sales of over $4 billion in 2024, and a market that continues to expand. DiMeo ¶¶ 3-4, 11; Jarosz ¶¶ 24, 53-56, 83-87. If MSN is permitted to launch before entry of final judgment in Novartis's favor on the '918 patent, MSN [redacted] and irreparably erode Entresto®'s market share, resulting in substantial losses to Novartis and [redacted]. *See* Ex. 14; DiMeo ¶¶ 5-11; Jarosz ¶¶ 24-28, 45-48, 80-82; *Natera*, at 1378 (lost market share supports irreparable harm); *Celsis In Vitro*

v.CellzDirect, 664 F.3d 922, 930-31 (Fed. Cir. 2012) (generic competition during growth stage is particularly damaging and supports irreparable harm). [redacted] *Abbott Labs. v. Sandoz*, 544 F.3d 1341, 1361-62 (Fed. Cir. 2008) (price erosion supports irreparable harm); *Sanofi-Synthelabo v. Apotex*, 470 F.3d 1368, 1382 (Fed. Cir. 2006) (same).

Further, [redacted] and if MSN were later withdrawn from the market, [redacted] Further, [redacted], harming Novartis's reputation and resulting in loss of goodwill. [redacted] These factors are difficult to predict and quantify, and will result in irreparable losses. Consistent with Novartis's irreparable harm here, the Federal Circuit previously granted Novartis an injunction pending appeal of the related '659 patent (CAFC No. 23-2218, D.I. 65, 121, 127), necessarily finding that MSN's at-risk launch would irreparably harm Novartis.

C. <u>The Balance of Hardships Favors the Grant of an Injunction</u>

Because Novartis prevailed on § 271(e)(2) infringement against MSN, § 271(e)(4)(A) provides statutory relief to Novartis requiring that MSN's effective ANDA approval date be reset to November 2026, after the '918 patent expires. Allowing MSN to launch, even for a short time, before its ANDA approval is reset, completely devalues Novartis's statutory right. By contrast, any potential injury to MSN from a temporary injunction is curable by a bond. Jarosz ¶¶ 14, 97.

Insofar as MSN alleges that it will lose a hypothetical "first-mover" advantage if a

preliminary injunction is granted, MSN was never entitled to launch its tablets before July 16, 2025; MSN does not have final approval due to Novartis's '659 patent exclusionary rights. A decision by this Court that MSN infringes the '918 patent claim 1—as compelled by the trial evidence—will further prevent MSN's launch until expiration of that patent on November 8, 2026. Regardless, the Court should grant Novartis a preliminary injunction because the harm to Novartis outweighs the potential harm to MSN. *See, e.g.*, *Ortho McNeil Pharm., Inc. v. Barr Labs., Inc.*, 2009 WL 2182665, at *10-11 (D.N.J. July 22, 2009) (granting preliminary injunction motion despite "some merit" to defendant's first-mover advantage argument).

D. The Public Interest Also Favors the Grant of a Temporary Injunction

There is a public interest in protecting Novartis's relief under 35 U.S.C. § 271(e)(4)(A). The Federal Circuit has recognized the "significant public interest in encouraging investment in drug development and protecting the exclusionary rights conveyed in valid pharmaceutical patents." *Sanofi-Synthelabo*, 470 F.3d at 1383-84. Providing such "exclusionary rights" encourages innovation; by not protecting those "exclusionary rights" there will be less incentive to develop new drugs, like Entresto®, that benefit the public. In addition, as discussed above, [redacted] are public harms that support the grant of an injunction. [redacted]

IV. CONCLUSION

Novartis's preliminary injunction motion pending entry of final judgment should be granted. Absent a decision on Novartis's motion before July 15, 2025, Novartis requests a temporary restraining order against MSN's at-risk launch. If the Court denies Novartis's motion or enters final judgment against Novartis, Novartis requests an injunction pending appeal under Rule 62(d)—or at least a 72-hour temporary injunction to seek relief from the Federal Circuit.

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VENABLE LLP

/s/ Daniel O'Brien
Daniel O'Brien (#4897)
1201 N. Market St, Suite 1400
Wilmington, Delaware 19801
(302) 298-3535
daobrien@venable.com

Attorneys for Plaintiff Novartis Pharmaceuticals Corporation

OF COUNSEL:

Nicholas N. Kallas
Christina Schwarz
Christopher E. Loh
Jared L. Stringham
VENABLE LLP
151 West 42nd Street
New York, New York 10036
(212) 307-5500
nkallas@venable.com
cschwarz@venable.com
cloh@venable.com
jlstringham@venable.com

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

In re Entresto (Sacubitril/Valsartan) Patent Litigation	C.A. No. 20-2930-RGA
NOVARTIS PHARMACEUTICALS CORPORATION, Plaintiff, v. MSN PHARMACEUTICALS INC., MSN LABORATORIES PRIVATE LIMITED, MSN LIFE SCIENCES PRIVATE LIMITED, GERBERA THERAPEUTICS, INC., NANJING NORATECH PHARMACEUTICAL CO., LIMITED, Defendants.	C.A. No. 22-1395-RGA

CERTIFICATE OF SERVICE

The undersigned counsel hereby certifies that true and correct copies of the foregoing document(s) were caused to be served on June 9, 2025 on the following counsel in the manner indicated below.

VIA EMAIL:

Stamatios Stamoulis
Richard C. Weinblatt
stamoulis@swdelaw.com
weinblatt@swdelaw.com
STAMOULIS & WEINBLATT LLC
800 N. West Street, Third Floor
Wilmington, DE 19801
(302) 999-1540

Ronald M. Daignault
Richard Juang
rdaignault@daignaultiyer.com
rjuang@daignaultiyer.com
DAIGNAULT IYER LLP
8618 Westwood Center Drive, Suite 150
Vienna, VA 22182

Kevin Warner
kwarner@rmmslegal.com
RAKOCZY MOLINO MAZZOCHI SIWIK LLP
6 West Hubbard Street, Suite 500
Chicago, IL 60654

Attorneys for Defendants MSN Pharmaceuticals Inc., MSN Laboratories Private Limited, and MSN Life Science Private Limited

Date: June 9, 2025

/s/ Daniel A. O'Brien
Daniel A. O'Brien (#4897)